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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,517	DUFT ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23-39 and 68-94* is/are pending in the application.

4a) Of the above claim(s) *25,26,28,35,36,69-71,73-75,77-79 and 85-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,27,29-34,37-39,68,72,76 and 80-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *122704 & 9204*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments and Responses

1) Acknowledgment is made of Applicants' amendments and responses filed 12/04/02, 11/19/04, 12/13/05, and 02/24/06 in response to the non-final rejection mailed 06/05/02.

Election of Species

2) Acknowledgment is made of Applicants' election of species filed 12/13/05 in response to the species election requirement mailed 10/26/05. Applicants have elected the species, SEQ ID NO: 14. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

Applicants state that the elected species reads upon claims 23, 24, 27, 29-34, 37-39, 41 (current claim 68), 45 (current claim 72), 49 (current claim 76) and 53-57 (current claims 80-84).

Status of Claims

3) Claim 1 was amended via the amendment filed 12/04/02.

Claims 16-47 were added via the amendment filed 12/04/02.

Claims 1-22 and 40 were canceled via the amendment filed 11/19/04.

Claims 23, 29, 30, 33, 35 and 38 were amended via the amendment filed 11/19/04.

New claims 41-67 have been added via the amendment filed 11/19/04.

Claims 25, 26, 33, 35, 36, 41-52 and 64-67 have been amended via the amendment filed 04/21/05.

Claims 41-67 have been canceled via the amendment filed 02/24/06.

New claims 68-94 have been added via the amendment filed 02/24/06.

Claims 23-39 and 68-94 are pending.

Claims 25, 26, 28, 35, 36, 69-71, 73-75, 77-79 and 85-94 have been withdrawn from consideration as being directed to a non-elected species. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 23, 24, 27, 29-34, 37-39, 68, 72, 76 and 80-84 are under examination.

Information Disclosure Statements

4) Acknowledgment is made of Applicants' information disclosure statements filed 12/27/04 and 09/02/04. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Declaration under 37 CFR 1.131

5) Acknowledgment is made of Applicants' submission of a declaration under 37 CFR 1.131 filed 09/02/04. It is stated that the declaration antedates the reference of Thompson *et al.* (May, 1997). However, since the currently examined new claims contain new matter, the instant claims are not granted priority to the prior application, and therefore the reference of Thompson *et al.* (May, 1997) still qualifies as prior art under 35 U.S.C § 102. See the new art rejection(s) set forth below.

Prior Citation of Title 35 Sections

6) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

7) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Specification/Claims

8) 37 CFR 1.75(d)(1) provides, in part, that 'the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.'

Claim 33 includes the limitation 'active anti-obesity agent' which lacks clear support or antecedent basis in the specification.

Rejection(s) Moot

9) The provisional rejection of claims 1-10 made in paragraph 13 of the Office Action mailed 08/04/00 and maintained in paragraph 15 of the Office Action mailed 06/05/02 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of the co-pending application, SN 09/870,762, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 1-10 made in paragraph 6 of the Office Action mailed 08/04/00 (paper no. 3) and maintained on page 3 of the Office Action mailed 04/20/01 (paper no. 6) and maintained in paragraph 16 of the Office Action mailed 06/05/02 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 1-10 made in paragraph 18 of the Office Action mailed 06/05/02 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 7-14 and 83-85 of the US patent 5,739,106, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 1-10 made in paragraph 19 of the Office Action mailed 06/05/02 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1-25 of the US patent 6,114,304 in view of Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claims 1-15 made in paragraph 21 of the Office Action mailed 06/05/02 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

14) The rejection of claims 1-14 made in paragraph 23 of the Office Action mailed 06/05/02 under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson *et al.* May, 1997), is moot in light of Applicants' cancellation of the claims.

15) The rejection of claims 1-3 and 11-15 made in paragraph 24 of the Office Action mailed 06/05/02 under 35 U.S.C § 102(b) as being anticipated by MacDonald *et al.* (*Diabetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) as evidenced by Robert *et al.* (WO 91/16917), is

moot in light of Applicants' cancellation of the claims.

16) The rejection of claims 1-6 and 11-15 made in paragraph 25 of the Office Action mailed 06/05/02 under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.* (*Diabetes* 46: 632-636, April 1997, already of record) (Thompson *et al.*, April, 1997) as evidenced by Guthrie *et al.* (US 4,443,619), is moot in light of Applicants' cancellation of the claims.

17) The rejection of claims 1-6 and 11-15 made in paragraph 26 of the Office Action mailed 06/05/02 under 35 U.S.C. § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in light of *The Random House Dictionary* (Ed. Flexner *et al.*, Random House, page 32, New York, 1984), is moot in light of Applicants' cancellation of the claims.

18) The rejection of claims 1-6 and 11-15 made in paragraph 27 of the Office Action mailed 06/05/02 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 95/07098) ('098), is moot in light of Applicants' cancellation of the claims.

19) The rejection of claims 1-6 and 11-15 made in paragraph 28 of the Office Action mailed 06/05/02 under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April 1996, already of record) (Kolterman *et al.*, 1996) in view of Robert *et al.* (WO 91/16917), is moot in light of Applicants' cancellation of the claims.

20) The rejection of claims 1-6 and 11-15 made in paragraph 29 of the Office Action mailed 06/05/02 under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) or Kolterman *et al.* (WO 95/07098) ('098) in view of Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997), or Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989), is moot in light of Applicants' cancellation of the claims.

21) The rejection of claims 1-3 and 11-15 made in paragraph 30 of the Office Action mailed 06/05/02 under 35 U.S.C § 103(a) as being unpatentable over Kong *et al.* (*Diabetologia* 40: 82-88, January 1997, Applicants' IDS) (Kong *et al.*, 1997), or MacDonald *et al.* (*Diabetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) in view of Robert *et al.* (WO 91/16917),

Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991) and Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997), or Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993), is moot in light of Applicants' cancellation of the claims.

22) The rejection of claims 1-6 and 11-15 made in paragraph 31 of the Office Action mailed 06/05/02 under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) ('098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in view of Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993) and Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991), is moot in light of Applicants' cancellation of the claims.

23) The rejection of claims 1-6 and 11-15 made in paragraph 32 of the Office Action mailed 06/05/02 under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) (Kolterman *et al.*, '098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April 1996, already of record) (Kolterman *et al.*, 1996) in view of Frishman *et al.* [*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997] and Jonderko *et al.* (*Israel J. Med. Sci.* 25: 20-24, 1989) (Jonderko *et al.*, 1989) or Guthrie *et al.* (US 4,443,619), is moot in light of Applicants' cancellation of the claims.

Response to Applicants' Arguments on Prior Art Rejection(s)

24) Applicants' arguments on the prior art rejections are moot in light of Applicants' cancellation of the claims. Only those of Applicants' arguments that are pertinent to the new rejection(s) set forth below are addressed herebelow.

Applicants cite case law and submit the following arguments the teachings of Kolterman *et al.* (April, 1996): (a) The Office has not discharged the burden of establishing that the allegedly inherent feature or features necessarily flow from the teachings of Kolterman *et al.* (April, 1996). (b) Kolterman *et al.* (April, 1996) say 'nothing about body weight, weight reduction', weight control, treatment of obesity, or treatment of obese individuals – let alone, as hypothesized by the

Office, improving the bodily appearance of individuals given pramlintide. (c) The paper concludes with no reference to weight or obesity, but only with the statement that the observations from the study will be extended in future studies to evaluate the extent to which amylin replacement can improve glucose control throughout the entire 24 h period. (d) As a matter of law this cannot establish inherency of the claimed methods of treating obesity, which can only be demonstrated by a showing that the methods are the inherent, inevitable result of the practice of another method. (e) Inherency may not be established by probabilities or possibilities. (f) In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

Applicants' arguments have been carefully considered, but are not persuasive. First, 'improving the bodily appearance of individuals given pramlintide' is not a hypothesis made by the Office as alleged, but is the definition provided in the instant application for the limitation 'treating obesity'. See paragraph 25(a) below. As explained under the art rejection set forth below), Kolterman *et al.* (April, 1996) did indeed teach a method of reducing body weight in diabetic human subjects by subcutaneous administration of 30 micrograms of pramlintide for four weeks (see Table 1 in particular). It should be noted in this regard that Applicants themselves have acknowledged that a decrease in body weight is detectable by two weeks of treatment (see last paragraph on page 10 of Applicants' response dated December 2002). At the end of four weeks of subcutaneously administered pramlintide treatment, Kolterman *et al.* (April, 1996) clearly demonstrated a detectable weight loss in the diabetic patients as depicted in Table 1.

It should further be noted that a 70 kg patient is not excluded from the scope of the instant invention, but is expressly included. For example, the recited amount range of 'about 0.01 to about 5 mg/day' of the amylin agonist, for example, pramlintide, is specifically "for a 70 kg patient". See lines 17-23 of page 27 of the instant specification; and lines 7-9 on page 13 of Applicants' response filed December 2002. This is important because the mean body weight $\pm$ SEM of Kolterman's (1996) diabetic placebo population was 74.5 ± 2.4 kg, whereas the mean body weight of the 15 diabetic patients administered subcutaneously with 30 micrograms of pramlintide, three times a day for 14 days, was 70.6 ± 2.7. Thus, Applicants' allegation that

Kolterman *et al.* (1996) says nothing about body weight or weight reduction in their patients is simply inaccurate. The structural limitations of the claims are clearly met by the teachings of Kolterman *et al.* (April, 1996). The very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al.* in 1996 in the very same patient population used by Applicants in Examples 2 or 3 (see also Table VI) of the instant application. The baseline BMI of less than 27.0 kg/m^2 as described by Applicants at lines 26 and 27 of page 35 of the instant specification was the same baseline BMI that Kolterman's (1996) Type I diabetic patients also had (see second full paragraph under the section 'Subjects, materials and methods' on page 493). The prior art method is the *same* as the instantly claimed method in terms of the amylin agonist (pramlintide) administered, the Type I diabetic patient population used, the subcutaneous route of administration, and the dose and the daily frequency of the amylin agonist administered. Therefore, Kolterman's (1996) method of subcutaneous administration of pramlintide to a Type I diabetic patient necessarily serves as the instantly claimed method of treating obesity and clearly anticipates the instantly claimed method. As a matter of law, Kolterman *et al.* (April, 1996) anticipates the instant invention. Irrespective of the mechanism(s) of action of the amylin agonist, pramlintide, and irrespective of whether amylin is a peripherally or centrally acting agent, whether or not pramlintide is an anorectogenic agent, gastric emptying-delaying agent, or a food intake suppressing agent, the prior art method necessarily serves as Applicants' method of treating obesity as defined in the instant application, i.e., 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance' for reasons identified above. See the art rejection set forth below.

Scope of Instant Invention

25) The instant invention encompasses within its scope the following:

(a) The limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12 of the specification.

(b) The limitation 'human subject' in the instant claims does not exclude 'a 70 kg

patient'. In fact, the now recited amylin or amylin agonist 'amount' of 'about 0.01 mg to about 5 mg per day' is indeed 'for a *70 kg patient*, administered in a single, divided or continuous doses' [Emphasis added]. See lines 17-23 on page 27 of the specification, as originally filed. See also lines 7-9 on page 13 of Applicants' response filed December 2002.

(c) The two human patient populations used in the insant application of treating obesity are patients with Type I diabetes mellitus and Type II diabetes mellitus. See Examples.

(d) A method of treating obesity by administering pramlintide to human diabetic subjects having a baseline body mass index (BMI) of not only at least 27.0 kg/m^2, but also a BMI of *less than 27.0* kg/m^2, is encompassed within the scope of the instant invention. See Example 3; Table VI; and lines 24-27 of page 35 of the specification, as originally filed.

New Rejection(s) Necessitated by Applicants' Amendments

The new rejection(s) set forth below are necessitated by Applicants' amendments, i.e., Applicants' submission of new claims.

Double Patenting

26) Instant claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of the co-pending application, SN 09/870,762. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the method of treating obesity claimed in the co-pending application falls within the scope of the instant claims.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

27) Claims 33, 34 and 82 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 64 and 68 of the US patent 6,956,026 (Beeley *et al.*,'026, filed 01/07/1997).

Although the conflicting claims are not identical, they are not patentably distinct from each other. There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist' [Emphasis added]. Absent a clear indication in the specification or claims of what the basic and novel

characteristics actually are, 'consisting essentially of', is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Beeley *et al.* ('026) taught a method of *reducing body weight* comprising peripheral administration of a therapeutically effective amount of an amylin agonist that falls within the scope of the instant claims and therefore anticipates the instant claims. The portion of the '026 disclosure at paragraph bridging columsn 14 and 15 which provides support for 'a therapeutically effective amount' does not exclude, but expressly includes an amount in the range of about 10 to 30 micrograms to about 5 mg/day, preferably about 30 to about 300 micrograms per day in a single or divided doses. The portion of the '026 disclosure that provides support for the subject being administered, includes a human having the obesity disorder (see paragraphs 2 and 3 in column 4).

28) Claims 33 and 82 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of the co-pending application, 10/851,574.

Although the conflicting claims are not identical, they are not patentably distinct from each other. There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist' [Emphasis added]. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of', is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

The method claimed in claim 6 of the co-pending application, 10/851,574, of *reducing body fat gain* in an overweight or obese human subject comprising administering to the human subject an amylin or amylin agonist falls within the scope of the instant claims and therefore anticipates the instant claims. The portion of the disclosure of the co-pending application, 10/851,574 that provides support for the amount or dose of amylin or amylin agonist, does not exclude, but expressly includes an amount in the range of from about 1 to 300 micrograms to about 5 mg/day (see paragraph above Example 1).

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

29) Claims 23, 24, 33 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al.* (already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

Although the conflicting claims are not identical, they are not patentably distinct from each other. There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist' [Emphasis added]. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of', is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

The method claimed in claims 34 and 35 of the US patent 5,686,411 is for the treatment of diabetes mellitus in a mammal comprising the administration to said mammal of a therapeutically effective amount of the amylin agonist of claim 19, i.e., ^{25,28,29}Pro-human amylin. The portion of the disclosure of the '411 patent at lines 45-53 in column 7 that supports the limitation mammal does not exclude, but expressly includes a patient seen by a medical practitioner, i.e., a human. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg of the agonist. The portion of the disclosure of the U.S. patent '411 at lines 9-12 of column 3 that describes the limitation 'diabetes mellitus' includes insulin-requiring diabetes mellitus. Given the art-known fact that upto 90% of diabetic patients are intrinsically obese as disclosed by Tsanev, the method of the '411 patent comprising the step of administration of a therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to a diabetic human anticipates the instant claims. Given that the method step of the '411 patent and the instant claims is the same, the method of the '411 patent is expected to bring about a therapeutic effect against the intrinsic obesity in the diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

30) Claims 23 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of the US patent 5,321,008 issued

to Beaumont *et al.* (already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract) and Rink *et al.* (US 5,739,106, already of record) ('106).

Although the conflicting claims are not identical, they are not patentably distinct from each other. There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist' [Emphasis added]. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of', is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

The method claimed in claim 11 and 13 of the US patent 5,321,008 is for the treatment of diabetes mellitus in an insulin-requiring mammal comprising the administration to said mammal of a therapeutically effective amount of a calcitonin alone, or calicitonin and insulin. The portion of the disclosure of the '008 patent at first full paragraph in column 13 supporting the limitation 'therapeutically effective amount' includes the typical dosage units of about 0.1 to 1 mg of calcitonin. Given the art-known fact that calcitonin is an amylin agonist as taught at line 4 of column 16 of Rink *et al.* ('106) and the art-known fact that up to 90% of diabetic patients are intrinsically obese as disclosed by Tsanev, the method of the '008 patent comprising the step of administration of a therapeutically effective amount of calcitonin to a type 2 diabetic human anticipates the instant claims. Given that the method steps of the '008 patent and the instant claims are the same, the method of the '008 patent is expected to bring about a therapeutic effect against the intrinsic obesity in the type 2 diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

31) Claims 23, 76 and dependent claims 24, 27, 29-32, 68, 80, 83 and 84 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 23 and 76 include the proviso language: 'with the proviso that the composition that the composition does not contain a cholecystokinin or a cholecystokinin agonist'. Applicants state that support for the proviso language excluding CCK and CCK agonists in the presently claimed invention can be found at least at page 9, lines 12-16 where US patent no. 5,739,106 is disclosed with claims directed to compositions of a cholecystokinin agonist and an amylin agonist or a hybrid molecule for use in controlling body weight. With this, Applicants state that one of ordinary skill in the art would understand that the instant claims would exclude the amylin/cholecystokinin agonist compositions and uses described in Patent No. 5,739,106. However, this does not provide descriptive support for this proviso language, which selectively excludes CCK and CCK agonists in the *presently claimed application*. Applicants also point to pages 14-21 and 25-28, and Examples 1-3 of the specification and state that none of the compositions contain a cholecystokinin or cholecystokinin agonist in combination with amylin or an amylin agonist. Applicants cite *In re Eickmeyer*, 602 F.2d 974, 981, 202 USPQ 655, 662-3 (CCPA 1979) and state that satisfaction of the description requirement is evident where an application contains 'sufficient disclosure, expressly or inherently, to make it clear to one skilled in the art that the appellant was in possession of the subject matter claimed and that one need not claim all that he is entitled to claim and need have support only for what he does claim. A method of treating obesity in a human subject as claimed comprising administering a composition that comprises an amylin or amylin agonist, or a peptide having an amino acid sequence of SEQ ID NO: 14, and which selectively excludes a choelcystokinin or cholecystokinin agonist, i.e., which comprises an amylin or amylin agonist, or a peptide having an amino acid sequence of SEQ ID NO: 14 plus any element other than the specifically recited choelcystokinin or cholecystokinin agonist, for example, bombesin or leptin, does not have inherent or express support on pages 14-21 and 25-28, and Examples 1-3 of the instant specification, as originally filed. The recited composition of narrower scope and its use in the claimed method lack descriptive support in the specification, as originally filed. The method as claimed wherein the specifically recited composition comprising an amylin or amylin agonist (but not comprising the specifically recited cholecystokinin or cholecystokinin agonist) 'effective to treat obesity' is not supported by the instant specification, as originally filed. Therefore, the above-identified limitations in the claims

are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to specific pages and lines that provide the descriptive support in the specification as originally filed, for the new limitations, or remove the new matter from the claim(s).

32) Claim 32 is rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 32 includes the limitation: 'about 15 minutes of said meal'. Applicants point to pages 14, 27-30 and 35, and Examples 1-3 of the specification and state that support for the new claim can be found therein. However, there appears to be no descriptive support for the above-identified phrase in these parts of the specification. Lines 10-11 on page 29 of the specification as originally filed include the limitation: 'within 15 minutes of each meal', but does not describe the limitation: 'about 15 minutes of... meal'. The scope of the limitations: 'within 15 minutes of each meal' and 'about 15 minutes of .... meal' are not the same. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to specific pages and lines that provide the descriptive support in the specification as originally filed, for the new limitations, or remove the new matter from the claim(s).

33) Claim 33 and dependent claims 34, 37-39, 72 and 82 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 33 includes the limitation: a composition comprising 'an active anti-obesity agent consisting essentially of an amylin or an amylin agonist, wherein the amount of amylin or amylin agonist administered is about 0.01 mg to about 5 mg per day'. Applicants state that support for the claim can be found at pages 14-21 and 25-28 and Examples 1-3. However, these parts of the specification do not include a recitation of 'an active anti-obesity agent' in a method of treating obesity consisting essentially of an amylin or an amylin agonist, wherein the amount of amylin or amylin agonist administered is about 0.01 mg to about 5 mg per day. The specification, as originally filed, does not provide a recitation of, or a description and/or definition for the limitation 'active anti-obesity agent' consisting essentially of .... Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to specific pages and lines that provide the descriptive support in the specification as originally filed, for the new limitations, or remove the new matter from the claim(s).

34) Claims 30, 81 and 83 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 30, 81 and 83 include the new amount range: 'an amount from about 0.0025 mg/dose to about 5 mg/dose' with regard to the administered amylin or amylin agonist. Applicants point to lines 17-21 of page 27 and lines 1-10 of page 28 of the specification and state that a total daily dose range of 0.01 mg to 5.0 mg given 1-4 times a day will yield a per administration dose range of a minimum of about 0.0025 mg/dose (given 4 times a day) to a maximum of about 5 mg (given 1 time a day). Lines 17-21 on page 27 of the specification do not support the newly recited range, instead describes a dose in the range of about 0.01 to about 5 mg/day for a 70 kg patient. Lines 1-10 of page 28 of the specification are limited to dosage

ranges of peptide agonists, for example, subcutaneously administered pramlintide, of 30-300 microgram doses given 1-4 times a day, more preferably 30-120 microgram doses given 2-4 times per day. This does not provide support for the now recited new range. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to specific pages and lines that provide the descriptive support in the specification as originally filed, for the new limitations, or remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

35) Claims 68, 72, 76, 83 and 84 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of treating obesity in a insulin-requiring type II diabetic human patient comprising subcutaneously administering to said patient a composition comprising 60 micrograms TID or QID of the amylin agonist analogue, pramlintide (see Examples 1 and 3), or a method of reducing insulin-induced weight gain in a type I diabetic human patient comprising subcutaneously administering to said patient a composition comprising 30 or 60 micrograms QID of the amylin agonist analogue, pramlintide, does not reasonably provide enablement for a method of treating obesity in any human subject comprising administering to said subject a composition comprising any peptide or any amylin agonist analogue comprising the amino acid sequence of SEQ ID NO: 14 as recited, wherein A1 is Lys, Ala, Ser, or hydrogen; B1 is Ala, Ser or Thr; C1 is Val, Leu or Ile; D1 is His or Arg; E1 is Ser or Thr; F1 is Ser, Thr, Gln, or Asn; G1 is Asn, Gln or His; H1 is Phe, Leu or Tyr; I1 is Ile, Val, Ala or Leu; J1 is Ser, Pro or Thr; K1 is Asn, Asp or Gln; X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage, wherein said intramolecular linkage comprises a disulfide bond, a lactam or a thioether linkage; and Z is an amino, alylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy; and provided that when A1 is Lys, B1 is Ala, C1 is Val, D1 is Arg, E1 is Ser, F1 is Ser, G1 is Asn, H1

is Leu, I1 is Val, J1 is Pro, and K1 is Asn; then one or more A to K1 is a D-amino acid and Z is selected from the group consisting of alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy, or such a composition with the proviso that the composition does not contain a cholecystokinin or a cholecystokinin agonist, effective to treat obesity, wherein the amount of the amylin agonist analogue administered is about 0.01 mg to about 5 mg per day, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant application, the nature of the invention is related to a method of treating obesity in a human subject comprising administering a peptide or amylin agonist analogue having the amino acid sequence of SEQ ID NO: 14 as recited, wherein A1 is Lys, Ala, Ser, or hydrogen; B1 is Ala, Ser or Thr; C1 is Val, Leu or Ile; D1 is His or Arg; E1 is Ser or Thr; F1 is Ser, Thr, Gln, or Asn; G1 is Asn, Gln or His; H1 is Phe, Leu or Tyr; I1 is Ile, Val, Ala or Leu; J1 is Ser, Pro or Thr; K1 is Asn, Asp or Gln; X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage, wherein said intramolecular linkage comprises a disulfide bond, a lactam or a thioether linkage; and Z is an amino, alylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy; and provided that when A1 is Lys, B1 is Ala, C1 is Val, D1 is Arg, E1 is Ser, F1 is Ser, G1 is Asn, H1 is Leu, I1 is Val, J1 is Pro, and K1 is Asn; then one or more A to K1 is a D-amino acid and Z is selected from the group consisting of alkylamino, dialkylamino,

cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy, or such a composition with the proviso that the composition does not contain a cholecystokinin or a cholecystokinin agonist, effective to treat obesity, wherein the amount of the amylin agonist analogue administered is about 0.01 mg to about 5 mg per day. The term 'human subject' encompasses diabetic and non-diabetic subjects. The amylin agonist analogue or the peptide of the recited structure of SEQ ID NO: 14 encompasses a large number of subsequence species or peptide variants of amylin or amylin agonist analogue species. Each of the species, or a representative number of the species encompassed within the scope of the instantly claimed method is required to be effective in treating obesity in a human subject when administered in the recited dose range. However, the instant specification does not show that these peptide variant or amylin agonist analogue species were administered to a human subject by any route, with or without cholecystokinin or cholecystokinin agonist, and that these species did have the ability to induce a therapeutic effect on obesity in said patients. Neither the specification nor the art at the time discloses that these peptide variants having a structure considerably different from that of amylin or pramlintide, did retain the obesity-relieving biologic function. In other words, the instant specification fails to demonstrate that the peptide variant species or the amylin agonist analogue species having the recited amino acid substitutions or chemical modifications, if administered by one of skill in the art to a diabetic or non-diabetic human subject by subcutaneous or non-subcutaneous route in the amount range recited, would elicit a therapeutic effect against obesity. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. In the instant application, there is no predictability that the recited peptide variants or amylin agonist analogues having the recited amino acid substitutions or chemical modifications would remain therapeutically functional as effective obesity relief agents in a human subject. This is critically important because the art in general reflects sensitivity of proteins, polypeptides, or peptides, to alteration of even a single amino acid residue in their amino acid sequences. The art establishes that an alteration in a single amino acid can eliminate or drastically change one or more functions of the polypeptide or peptide, including the receptor binding activity. For instance, Burgess *et al.* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the

substantial loss of heparin binding, receptor binding, and biological activity of the protein. Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) provided similar teachings and showed that in the protein, transforming growth factor alpha, replacement of aspartic acid with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that a peptide or amylin agonist analogue molecule having the recited number of amino acid substitutions, or chemical modifications would have its primary, secondary or tertiary structure unchanged and would have its obesity-relieving therapeutic activity and the receptor recognition activity retained. The effects of such amino acid substitutions upon the peptide structure and biologic/therapeutic function(s) are unpredictable. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a peptide, with the recited amino acid substitutions in the peptide or amylin agonist analogue of SEQ ID NO: 14, the therapeutic or obesity-relieving function and the receptor binding function of the peptide variants or amylin agonist analogues could not be predicted, nor would it be expected to be the same as that of amylin or pramlintide. One simply cannot predict what effects a given amino acid substitution, or one or more chemical modifications in the amino acid sequence would cause, and therefore a method of treating obesity by administering such a modified molecule is not enabled as Applicants' invention. Clearly, Applicants have not enabled the full scope of the invention as claimed. The above-identified unpredictability is particularly true in case of amylin. Similar to the art-recognized unpredictability associated with even a single amino acid change/substitution and the coupling efficiency of the resultant amylin analog or analog mimic (see last paragraph under 'Detailed

Description of the Invention' of Albrecht, WO 92/15317), there is unpredictability associated with the effect of one or more of the amino acid substitutions in the peptide species or the amylin agonist analogue species encompassed within the scope of claims 68, 72, 76, 83 and 84 on the obesity-relieving function of the amylin agonist analogue or the peptide variant species. The art on amylin at the time of the invention documented the existence of species specificity with regard to one or more of amylin's biologic functions. Arnelo *et al.* (*Scand. J. Gastroenterol.* 31: 83-89, 1996, already of record) showed that while chronic administration of rat amylin resulted in prolonged inhibitory effects on food intake and reduced body weight in rats, the human amylin had no effect (see abstract) indicating the occurrence of host species specificity. This occurred despite a high degree of sequence identity between rat amylin and human amylin. See Figure 1 of Cooper *et al. Biochim. Biophys. Acta* 1014: 247-258, 1989. Similarly, Chance *et al.* (*Brain Res.* 539: 352-354, 1991, already of record) showed that while 0.2 microgram of rat amylin reduced feeding significantly, 2.0 milligrams of human amylin was without effect. Chance *et al.* stated that although the absence of effect of human amylin may appear surprising since there is a difference in homology of only 6 amino acids, three of these amino acids in the rat amylin molecule are proline, which may confer 'major differences in structure and receptor recognition' (see left column on page 353). An enabling disclosure or showing with the recited peptide variants or amylin agonist analogues becomes critically necessary in the instant application under the provision of 35 U.S.C § 112, first paragraph, particularly in view of Applicants' current argument/theory that amylin's therapeutic effect on obesity is allegedly not obligatorily linked to, an effect on food intake (see page 3 of the October 2001 Young Declaration; and pages 10 and 11 of Applicants' response filed December 2002). Applicants have not enabled within the instant application a method of treating obesity in a human subject by administering a peptide variant or amylin agonist analogue of the amino acid sequence of SEQ ID NO: 14 which has the unique function of *selectively* inducing weight loss in said subject without having a food intake-reducing effect. There is no showing within the instant invention that the peptide variants or the amylin agonist analogues encompassed within the scope of the instant claims, with or without cholecystokinin or cholecystokin agonist, were indeed therapeutically effective in a method of treatment of obesity in a diabetic or non-diabetic human patient. The only amylin agonist species that is described as

appearing to reduce insulin-induced weight gain in diabetic patients is pramlintide (see lines 22 and 23 on page 31 of the instant specification).

For the reasons delineated above, the practicing of the full scope of the instant invention using the recited peptide variant species or the amylin agonist analogue species is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of skill in the art at the time of the effective filing date of the instant application to reproducibly practice the full scope of the invention as claimed, due to the lack of specific guidance and direction, the lack of enabling disclosure with regard to the full scope, the art-demonstrated functional unpredictability of peptide variants, including amylin variants as recognized in the state of the art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

36) Claims 24, 27, 29-34, 37-39, 68, 72, 76 and 81-84 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 24, 27 and 29-32 lack proper antecedent basis in the limitation: 'A method according to claim ...'. For proper antecedence and consistency with claims 80-82, it is suggested that Applicants replace the limitation with --The method according to claim ....--.

(b) Analogous rejection and criticism applies to claims 34 and 37-39.

(c) Claim 33 is vague and/or indefinite in the limitation 'active anti-obesity agent' because it is unclear what does the term 'active' encompass with regard to the recited 'anti-obesity agent'. It is unclear how does an 'active anti-obesity agent' differ in scope or structure from an 'anti-obesity agent'.

(d) Claims 68, 72 and 76 are confusing in the limitation 'an amino acid sequence of (SEQ ID NO:14)', because it is unclear what is included or excluded by the claim language or the parenthesis. Does the recited amylin agonist analogue or the recited peptide comprise any amino acid sequence of SEQ ID NO: 14, i.e., any smaller amino acid sequence, for example, Val-Gly-Ser from within SEQ ID NO: 14?

(e) Claims 34, 37-39, 68, 72 and 81-84, which depend directly or indirectly from claim 33, 24 or 76, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

37) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(e)** the invention was described in-
> **(2)** a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

38) Claims 23, 24, 27, 29, 30, 33, 34, 37, 38 and 80-82 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Beeley *et al.* (US 6,956,026, filed 01/07/1997).

The use of the limitation 'polypeptide consisting *essentially* of a polypeptide' in claim 33 has been noted. MPEP § 2111.03 states that claims recited in 'consisting essentially of' language should be construed as if recited in open 'comprising' language, absent some evidence that the additional ingredients in the prior art process/product materially affect the basic and novel characteristics of the claimed invention. There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist'. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355 ('PPG could have defined the scope of the phrase 'consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.'). See also *In re Janakirama Rao*, 317 F.2d 951, 954, 137 USPQ 893, 895-896 (CCPA 1936).

Beeley *et al.* taught a method of reducing food intake or reducing appetite in a subject desirous or in need of reducing food intake or *reducing body weight* comprising subcutaneous administration of a pharmaceutical composition comprising a therapeutically effective amount of an amylin agonist, i.e., a composition that did not contain cholecystokinin or cholecystokinin agonist.

The subject is human. See claims, particularly claims 1, 3, 10, 16, 19, 26, 32, 33, 35, 42, 46, 47, 49, 56, 60, 61, 63, 64, 65, 67 and 68. Beeley *et al.* taught a method of treating conditions or disorders which can be alleviated by reducing food intake, or a condition or disorder in which the reduction of food intake is of value, including *obesity*, eating disorders, or type II diabetes, comprising administration of an effective amount of a composition comprising a compound that affects satiety, such as, an amylin agonist. Beeley's method is useful for reducing the appetite and reducing the weight of the subjects (see 'Field of the Invention'). The method involves the administration of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more of a compound that exhibits a long term or short-term satiety action, such as, amylin, an amylin agonist, for example, pramlintide or AC-137 or ^{25,28,29}Pro-human amylin. The composition is a *single* composition comprising amylin or amylin agonist, and the composition is advantageously administered separately from extendin or extendin agonist (see first, third and fourth full paragraphs in column 5; and third full paragraph in column 13). Thus, the prior art composition that comprises one amylin agonist compound exhibiting a long term or short-term satiety action, such as, pramlintide, does not contain cholecystokinin or cholecystokinin agonist, or consists essentially of the amylin agonist. The prior art method that comprises the separate administration of a single amylin or amylin agonist composition meets the active administration step of the instantly claimed method. The pharmaceutical composition is administered subcutaneously (see lines 34-37 in column 14). Beeley *et al.* further taught that a suitable administration format may be best determined by a medical practitioner for each patient individually as described in standard formulation treatises, e.g., *Remington's Pharmaceutical Sciences* by EW Martin (see lines 32-42 in column 13). The typical effective daily dose of the compound is in the range of 10 micrograms to 5 mg per day, or about 30 to about 500 micrograms to 5 mg per day, administered in a single or divided doses (i.e. more than one doses per day). Beeley *et al.* further taught that the exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above-quoted range, as well upon the age, weight and condition of the individual. Beeley *et al.* taught that administration should begin whenever the suppression of food intake, or weight lowering is desired, for example, at the first sign of symptoms or shortly after diagnosis of *obesity*, diabetes

mellitus, or insulin resistance syndrome. See paragraph bridging columns 14 and 15.

The required active step of the instantly claimed method is clearly met by the prior art method in that pramlintide is subcutaneously administered to a human subject in whom weight lowering is desired. The structural limitations of the claimed method are met by the disclosure of Beeley *et al.*, and therefore instant claims 23, 24, 27, 29, 30, 33, 34, 37, 38 and 80-82 are anticipated by Beeley *et al.*

39) Claims 23, 24, 29, 30, 33, 34, 37, 38 and 80-82 are rejected under 35 U.S.C § 102(b) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al.*, May, 1997).

Instant claims are granted the effective filing date of the instant invention (12/06/1999) because of the new matter identified above.

It is noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12.

Thompson *et al.* (May, 1997) taught a method of subcutaneous administration of pramlintide composition, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose of 30 or 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) for a period of four weeks. Thompson's (May, 1997) pramlintide composition did not comprise cholecytokinin or cholecystokinin agonist, but consisted essentially of pramlintide. The method carried out with a dose of 60 micrograms of pramlintide TID or QID not only improved glycaemic control in these patients, but also decreased body weight (see abstract). Thompson's (May, 1997) method clearly decreased the body weight of the treated patients and therefore, improved the bodily appearance of the treated patients, and thus necessarily served as a method of treating obesity as defined in the instant application.

Claims 23, 24, 29, 30, 33, 34, 37, 38 and 80-82 are anticipated by Thompson *et al.* (May, 1997).

40) Claims 23, 24, 29, 30, 31, 33, 34, 37-39 and 80-82 are rejected under 35 U.S.C § 102(b)

as being anticipated by Thompson *et al.* (*Diabetologia* 40: 1278-1285, November 1997, already of record) (Thompson *et al.*, November, 1997).

Instant claims are granted the effective filing date of the instant invention (12/06/1999) because of the new matter identified above.

It is noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12.

Thompson *et al.* (November, 1997) taught a method of subcutaneously administering, prior to meals, 30 micrograms three or four times a day, or 60 micrograms two times a day, of pramlintide, an analogue of the human hormone amylin, to patients with IDDM for a period four weeks. Thompson's pramlintide composition did not comprise cholecytokinin or cholecystokinin agonist, but consisted essentially of pramlintide. See summary; Subjects and methods; and Results sections. While the body mass index of the placebo group was 25.2 ± 0.5, the BMI of the patients treated with 30 micrograms of pramlintide TID was lower, i.e., 24.6 ± 0.6 or 24.7 ± 0.5 kg/m^2 (see Table 1). Thompson's (November, 1997) method clearly decreased the body weight of the treated patients and therefore, improved the bodily appearance of the treated patients, and thus necessarily served as a method of treating obesity as defined in the instant application.

Claims 23, 24, 29, 30, 31, 33, 34, 37-39 and 80-82 are anticipated by Thompson *et al.* (November, 1997).

41) Claims 23, 24, 29-31, 33, 34, 37-39 and 80-82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996).

It is noted that the 'human subject' recited in the instant claims encompasses both insulin-taking and non-insulin-taking human subject. It is further noted that the instant invention encompasses, i.e., does not exclude, a weight loss in a human subject having a baseline BMI of less than 27.0 kg/m^2 (see lines 24-27 of page 35 of the instant specification).

It is noted that a 70 kg patient is not excluded from the scope of the instant invention, but is expressly included. For example, the recited amount range of 'about 0.01 to about 5 mg/day'

of amylin agonist, for example, pramlintide to be administered, is specifically "for a 70 kg patient". See lines 17-23 of page 27 of the instant specification; and lines 7-9 on page 13 of Applicants' response filed December 2002.

It is further noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12.

Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e., $^{25, 28, 29}$pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days (see abstract; and page 493). Kolterman's pramlintide composition did not comprise cholecytokinin or cholecystokinin agonist, but consisted essentially of pramlintide. Similar to the baseline BMI of less than 27.0 kg/m^2 described by Applicants at lines 24-27 of page 35 of the instant specification, Kolterman's (1996) patients had a BMI of less than 27.0 kg/m^2 (see second full paragraph under the section 'Subjects, materials and methods' on page 493). Kolterman's (1996) patients who were treated with 30 micrograms of subcutaneously administered pramlintide showed a lower body weight of 70.6 $\pm$ 2.7 kg compared the placebo controls whose body weight was about 4.0 kg higher, i.e., 74.5 $\pm$ 2.7 kg (see Table 1). It should be noted that a 70 kg patient is not excluded from the scope of the instant invention, but is expressly included. For example, the recited amount range of 'about 0.01 to about 5 mg/day' of amylin agonist, for example, pramlintide, is specifically "for a 70 kg patient". See lines 17-23 of page 27 of the instant specification; and lines 7-9 on page 13 of Applicants' response filed December 2002. This is important because the mean body weight $\pm$ SEM of Kolterman's (1996) diabetic placebo population was 74.5 $\pm$ 2.4 kg, whereas the mean body weight of the 15 diabetic patients administered subcutaneously with 30 micrograms of pramlintide, three times a day for 14 days, was 70.6 $\pm$ 2.7. Thus, Kolterman's (1996) method did reduce the body weight of the human diabetic subjects administered 30 micrograms of pramlintide, and therefore, improved the bodily appearance of the treated patients, and thus necessarily served as a method of treating obesity as defined in the instant application.

Irrespective of the mechanism(s) of action of the amylin agonist pramlintide and irrespective of whether amylin is a peripherally or centrally acting agent, whether or not pramlintide is an anorectogenic agent, gastric emptying-delaying agent, or a food intake suppressing agent, the prior art method necessarily serves as Applicants' method of treating obesity as defined in the instant application, i.e., 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance'.

Claims 23, 24, 29-31, 33, 34, 37-39 and 80-82 are anticipated by Kolterman *et al.* (1996).

42) Claims 23, 24, 27, 29-31, 33, 34, 37-39 and 80-82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 96/40220, already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

Instant claims are granted the effective filing date of the instant invention (12/06/1999) due to the new matter identified above.

It is noted that the weight loss occurring in those patients having a baseline BMI of even 'less than 27.0 kg/m^2' following pramlintide administration is not excluded, but is clearly included within the scope of the instant invention. See lines 24-27 of page 35 and Table IV of the instant specification. The patient population used in the instant invention to treat obesity by the administration of the recited amount of pramlintide is insulin-requiring Type 2 diabetics (see Example 1).

There is no indication in the instant specification of what is being excluded by the language 'active anti-obesity agent consisting *essentially* of an amylin or an amylin agonist' [Emphasis added]. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of', is construed as equivalent to 'comprising'. See e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Kolterman *et al.* ('220) taught a method of administering to an insulin-taking type II diabetic subject a composition comprising a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist, pramlintide or $^{25, 28, 29}$pro-h-amylin, also known as AC137. The composition does not comprise a cholecystokinin or cholecystokinin agonist, but consists essentially of pramlintide. See pages 9-11; paragraph bridging pages 20 and 21; page 21; and first paragraph in page 19. Pramlintide is

administered subcutaneously 1-4 times a day before meals (see pages 9 and 22). Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus' (see page 10). Thus, the very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al.* ('220) in 1996 in the very same patient population used by Applicants in Example 1 of the instant application. Given Kolterman's ('220) express teaching that obesity is a characteristic of 'most patients with Type II diabetes mellitus', Kolterman's ('220) method of subcutaneous administration of pramlintide to a Type II diabetic patient in an amount that falls within the range recited in the instant claims necessarily serves as the claimed method of treating obesity and therefore anticipates the instantly claimed method. The prior art method is the *same* as the instantly claimed method in terms of the amylin agonist (pramlintide) administered, the insulin-taking Type II diabetic patient population used, the subcutaneous route of administration, the dose and the daily frequency of the amylin agonist administered, and the administration step prior to a meal. Since the structural limitations of the instant claims are clearly met by the teachings of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve as the instantly claimed method and is expected to bring about the same therapeutic effect.

The Office's position that Kolterman's ('220) method is the same as the Applicants' claimed method is based upon the fact that the method step, the product administered, the amount of the product administered, and the route by which the product is administered, and the human patient population to which the product is administered, are overlapping in the two methods. There is sufficient overlap between the the prior art method and the Applicants' method to reasonably conclude that Kolterman's ('220) method is one and the same as the Applicants' method. Given the art-known fact that upto 90% of diabetic patients are intrinsically obese as disclosed by Tsanev, Kolterman's ('220) method comprising the step of administration of a therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to a type 2 diabetic human anticipates the instant claims. Given that the method step of the Kolterman's ('220) method and the instant claims is the same, Kolterman's ('220) method is expected to bring about a therapeutic effect against the intrinsic obesity in the diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in

the diabetic patients.

Since the Office does not have the facilities for examining and comparing Applicants' claimed method with that of the prior art, the burden is on Applicants to show a novel difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. MPEP 2112 refers to *In Re Best* to explain that something which is old does not become patentable upon the discovery of a new property; 'the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)'. Since the prior art clearly teaches the claimed method, any assertions of specific functional properties attributed to the amylin or amylin agonist in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 23, 24, 27, 29-31, 33, 34, 37-39 and 80-82 are anticipated by Kolterman *et al.* ('220).

Relevant Art

43) The art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Szabo *et al.* (*Vnitr Lek* 44: 145-150, March 1998) taught that up to 90% of type II diabetic (NIDDM) patients are obese (see abstract).
- Mack *et al.* (US 20050197287 A1) expressly disclose that in humans, 'patients who are overweight or obese are considered those with a Body Mass Index or BMI of equal to or greater than 25'. See lines l-3 in section [0004]. Mack *et al.* teach that according to the NIH Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, all adults who have a 'BMI of 25 or more' are considered at risk for premature death and disability as a consequence of overweight and obesity. See section [0005].
- Arnelo *et al.* (*Am. J. Physiol.* 271: R1654-R1659, 1996, already of record) taught the anorectic effect of IAPP in rats. Arnelo *et al.* taught that *subcutaneously* administered IAPP dose-dependently inhibited food intake and decreased body weight gain. Arnelo *et al.* taught that IAPP may play an important physiological or pathophysiological role in control of food intake

(see abstract).

- Arnelo *et al.* (*Scand. J. Gastroenterol.* 31: 83-89, 1996, already of record) showed that chronic increase of circulating IAPP levels can cause a marked reduction in both food intake *and* body weight in rats (see abstract).

- Morley *et al.* (*Peptides* 12: 865-869, 1991, already of record) showed that amylin decreased food intake both in diabetic and non-diabetic mice (see abstract; and Figures 1 and 2).

- Andrew Young *et al.* (*Nutrition* 14: 524-527, June 1998) must be noted [Emphasis added]:

> Several groups have reported an effect of amylin to inhibit food intake.[28-30] This effect is as potent as that of cholecystokinin (CCK), the prototypic peripheral satiety agent ...
>
> ... amylin, via its hormonal actions, may be relevant to the treatment of both forms of diabetes, ... potently inhibits gastric emptying. .... Of peptides known to be secreted in response to ingested carbohydrate, only amylin .... reported to inhibit gastric emptying at near-physiologic concentrations, [19]
>
> Amylin reduces food intake in rodents. This action, which synergizes with a similar action of CCK, could reflect a role as short-term peripheral satiety agent. **Amylin alone** or in combination with CCK may be useful in moderating caloric intake in **obesity** and other metabolic disorders.
>
> In different studies, pramlintide has been shown to slow gastric emptying in man[17].
>
> Amylin is the most potent mammalian inhibitor of gastric emptying identified thus far[19]. ... amylin is a physiologic regulator of gastric emptying.

- A.A. Young *et al.* (*Nutrition* 45: 1-3, January 1996) taught the dose-dependent slowing of gastric emptying by *subcutaneously* administered amylin or cholecystokinin in a rodent model (see pages 1-2 and Figure 1). A.A. Young *et al.* taught that amylin is the most potent inhibitor of gastric emptying (see page 3).

- Claim 3 of US 5,175,145 issued to Garth Cooper of Amylin Pharmaceuticals identified CGRP is an amylin agonist that has amylin activity as opposed to an amylin antagonist.

- EP 0 408 294 A2 refers to CGRP 8-37 as 'the amylin agonist CGRP 8-37' (see line 38 on page 8).

- Scherbaum WA (*Exp. Clin. Endocrinol. Diabetes 106*: 97-102, 1998) taught that people with both type 1 *and* type 2 diabetes are 'amylin deficient' (see first full paragraph in left column on page 99).

- Despite the existence of the US patents 5,280,014 and 5,364,841, Rink *et al.* (US 5,739,106) used an amylin agonist such as $^{25, 28, 29}$pro-h-amylin in a method for *control of body weight* in a mammal including a human (see claim 85 and second full paragraph in column 7).

Rink *et al.* expressly acknowledged the previously known biologic properties of amylin such as food intake-reducing and anorectic effects (see paragraph bridging columns 6 and 7). Rink *et al.* expressly taught that an amylin agonist-containing therapeutic composition is useful in the claimed methods of controlling appetite and/or *control of body weight* (see third full paragraph in column 7). An amylin agonist is defined herein as a compound having 'one' or more of the known biological activities of amylin, in particular the 'ability to reduce food intake'.

- Well before the filing date of the instant application, well before the effective filing date of the US patent 5,739,106, and well before the issuance of US patents 5,280,014 and US 5,364,841, Balasubramaniam *et al.* (WO 94/26292, already of record) disclosed several amylin analogs that behave as amylin agonists and exhibit an appetite suppressant effect. Balasubramaniam *et al.* taught that amylin serves as an *anorectic agent* (see lines 8 and 9 of page 3), while amylin antagonists *increase* appetite (see abstract; and last paragraph on page 21). Most importantly, Balasubramaniam *et al.* expressly taught in 1994 that '**amylin agonists are useful for treating problems of overweight**'. Balasubramaniam *et al.* expressly suggested the administration of amylin agonists to a ***human*** by one of the traditional modes, including parenteral mode, for the **treatment of obesity** (see lines 11 and 12 on page 9; last paragraph on pages 21 and 22) [Emphasis added]. Balasubramaniam *et al.* further taught a method of controlling food intake in a human comprising administering to said human a therapeutic amount of an amylin analog (see claim 13). Clearly, Balasubramaniam *et al.* suggested amylin agonists as anti-obesity agents in 1994.

- Kosmiski *et al.* (*Curr. Opin. Endocrin. Diabet.* 4: 36-39, 1997) reviewed the impact of appetite suppressant therapy on both weight loss and metabolic parameters in patients with NIDDM (see abstract). Kosmiski *et al.* taught that 'the majority of patients with NIDDM are obese' and that 'reduction of body weight is therapeutic in obese patients with NIDDM'. Kosmiski *et al.* taught that '[n]umerous studies have indeed shown that appetitie suppressants reduce body weight in obese NIDDM patients' (see page 36).

Remarks

44) Claims 23, 24, 27, 29-34, 37-39, 68, 72, 76 and 80-84 stand rejected.

45) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

46) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number (571) 273-8300, which receives facsimile transmissions 24 hours a day and 7 days a week.

47) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

48) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

S. Devi 5 May 06
S. DEVI, PH.D.
PRIMARY EXAMINER